Predicting Systems Behaviors in PK and PD Using Biologically Based Modeling of Rats & Mice

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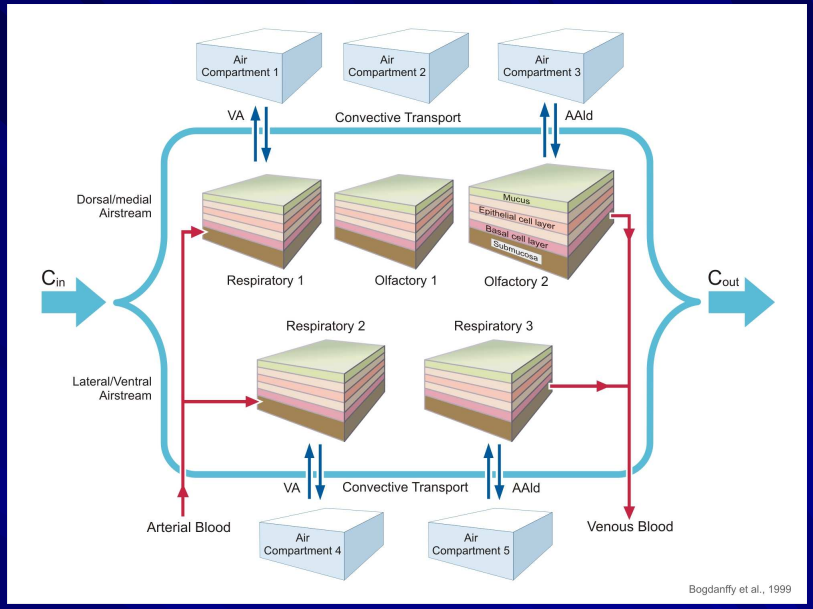
Outline

- Biological Modeling Contexts
- Predicting PK
- Predicting PD
- Regulatory Acceptance of Models
- Conclusions

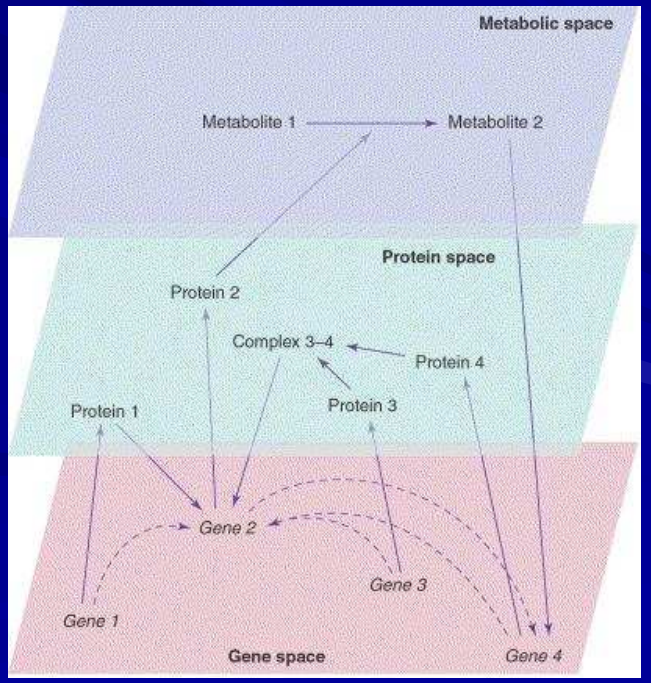
This presentation represents the views of the presenter and does not necessarily reflect official US EPA policy.

What is a biologically based model?



Bogdanffy et al. A biologically based risk assessment for vinyl acetate-induced cancer and noncancer inhalation toxicity.Toxicol Sci. 1999 51(1):19-35.

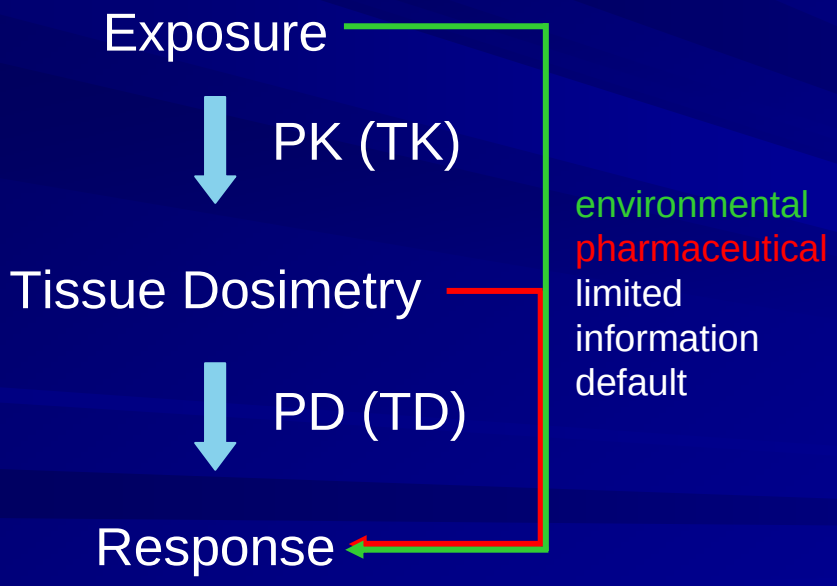
- Explicit mathematical representation of biological hypotheses, knowledge of the physical system
  - Simplification vs. Completeness
  - Levels of biological organization
- Biological & Association Models Systems Biology & Bioinformatics

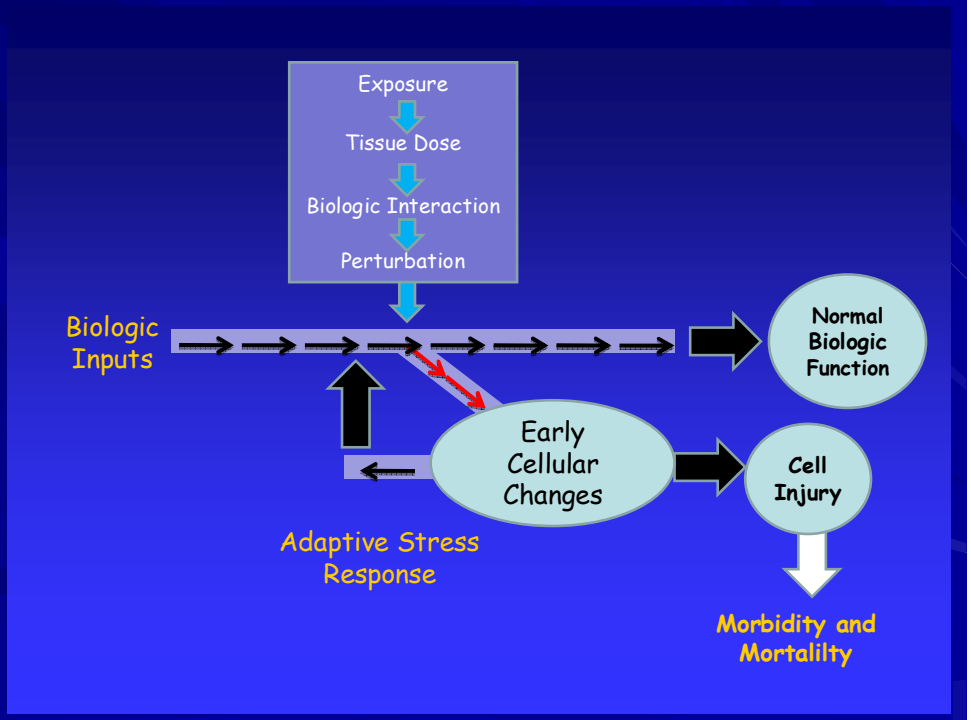


Brazhnik P, de la Fuente A, Mendes P. Gene networks: how to put the function in genomics.Trends Biotechnol. 2002 20(11):467-72

Model Context

- Toxicological Context: Environmental Source to Outcome Continuum
- Mode of Action (EPA Cancer Guidelines effectively define as PD)
- Toxicity Pathway *(National Academy of Sciences 2007 Toxicity Testing in the Twenty-first Century: A Vision and a Strategy)*
- Problem Formulation for specific model



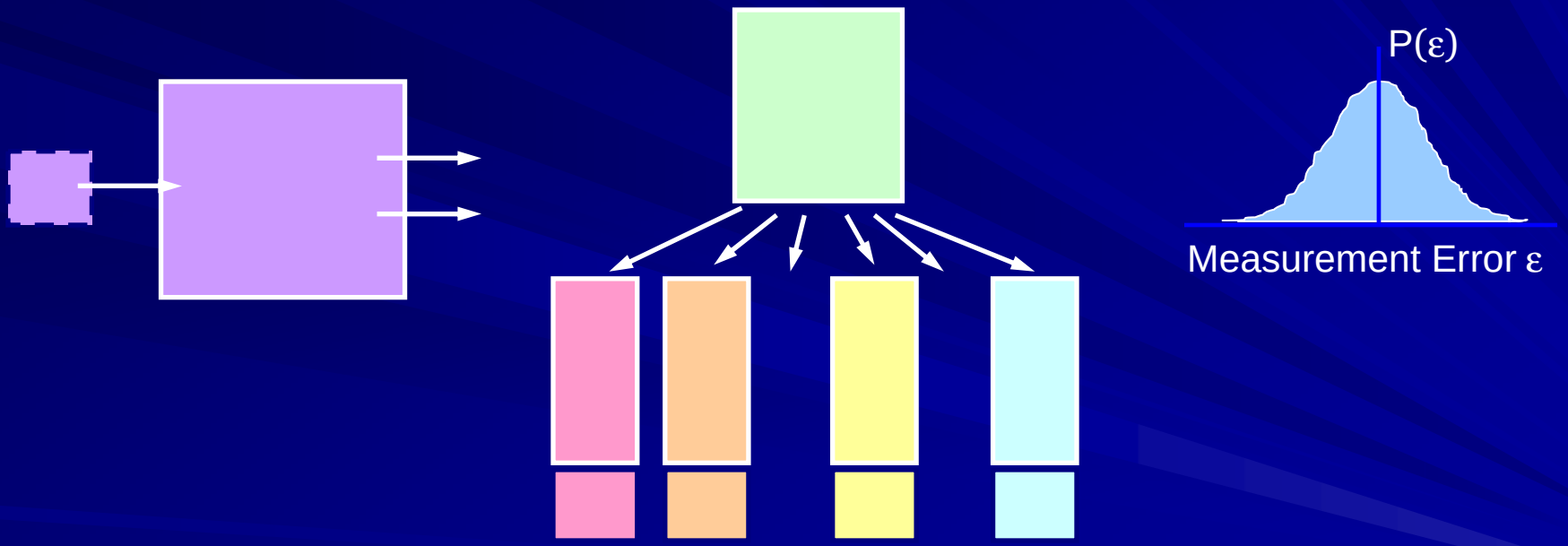


Models for full characterization of variability and uncertainty

PK and/or PD Model

Hierarchical Statistical Model

Measurement Model



Estimate all parameters simultaneously.

Predicting PK

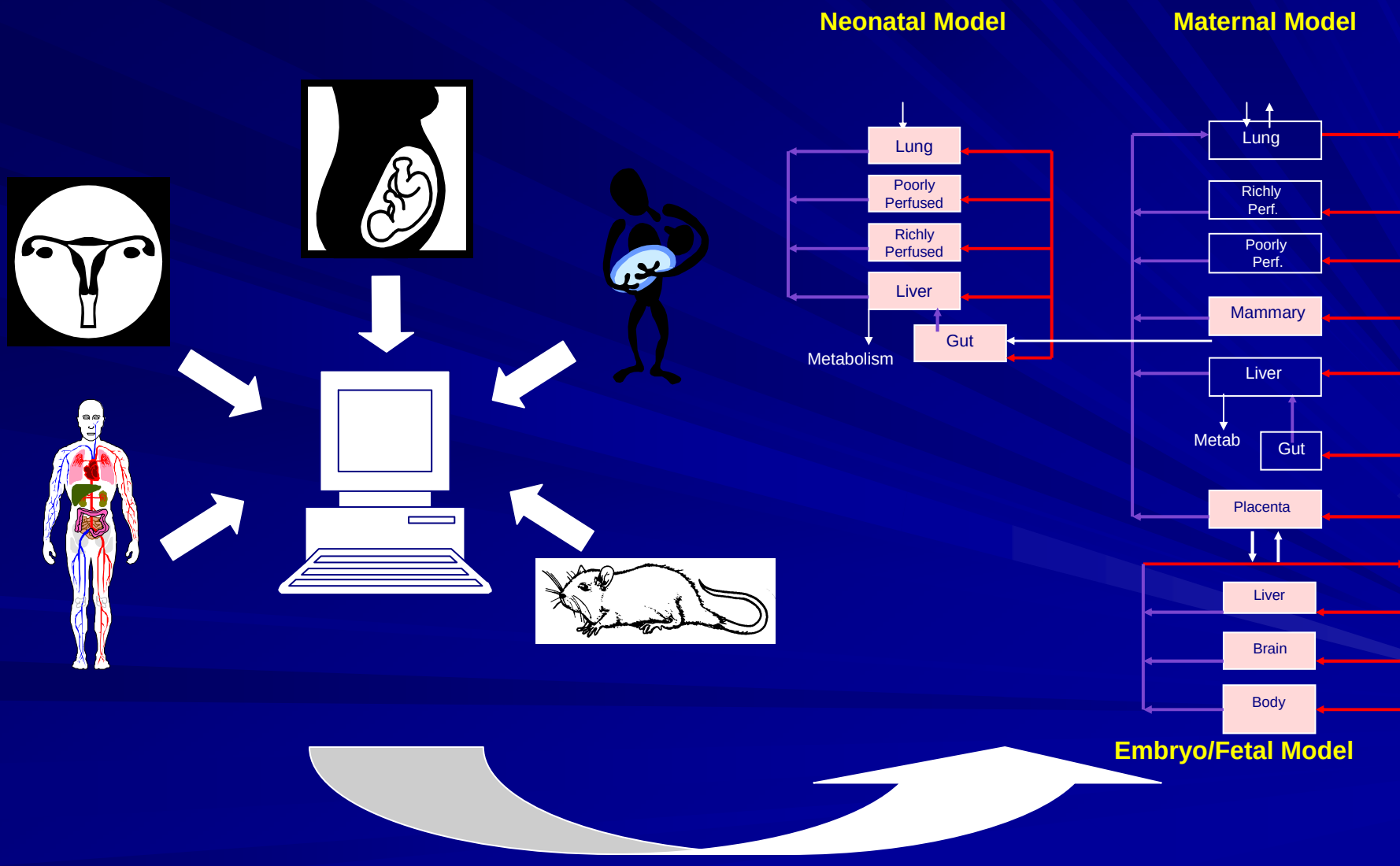
- Biologically based pharmacokinetic models
  - Analysis tools
  - Predictive tools
- Across exposure conditions (e.g., route-to-route extrapolation; acute duration adjustments, exposure doses/concentrations)
- Ages & lifestages (e.g., pregnancy, lactation)
- Predicting in vivo from in vitro data (e.g., across species, human polymorphism, ages, chemicals)

Predicting PK

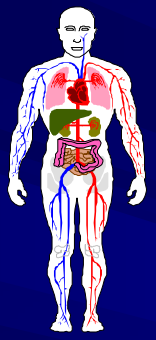
- Lactational transfer and toxicity study exposure methods
- Perfluorinated compounds
- Changes in VOC PK with age

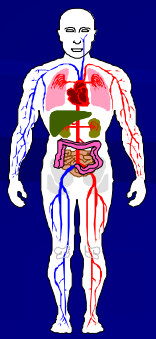
Barton HA. Computational pharmacokinetics during developmental windows of susceptibility. J Toxicol Environ Health A. 2005 11-25;68(11-12):889-900

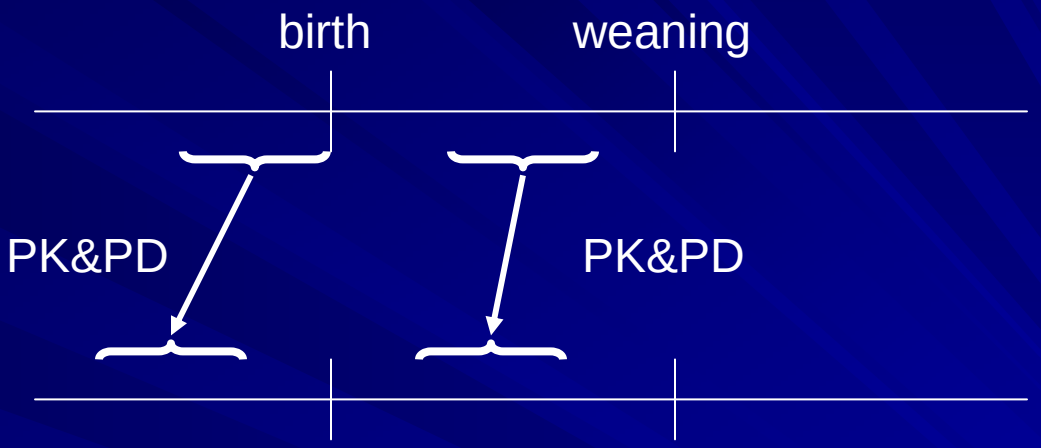
Predicting Across Sensitive Populations, Lifestages, Species

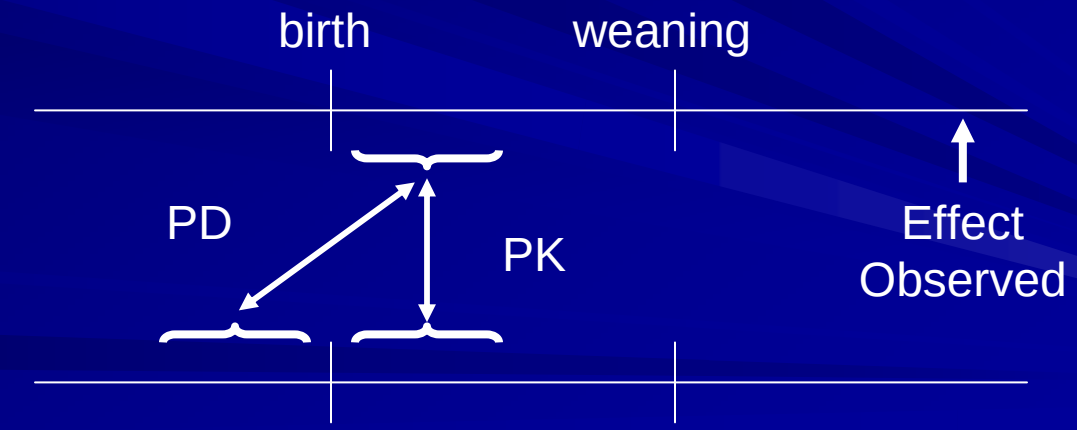


Mapping Cross-species





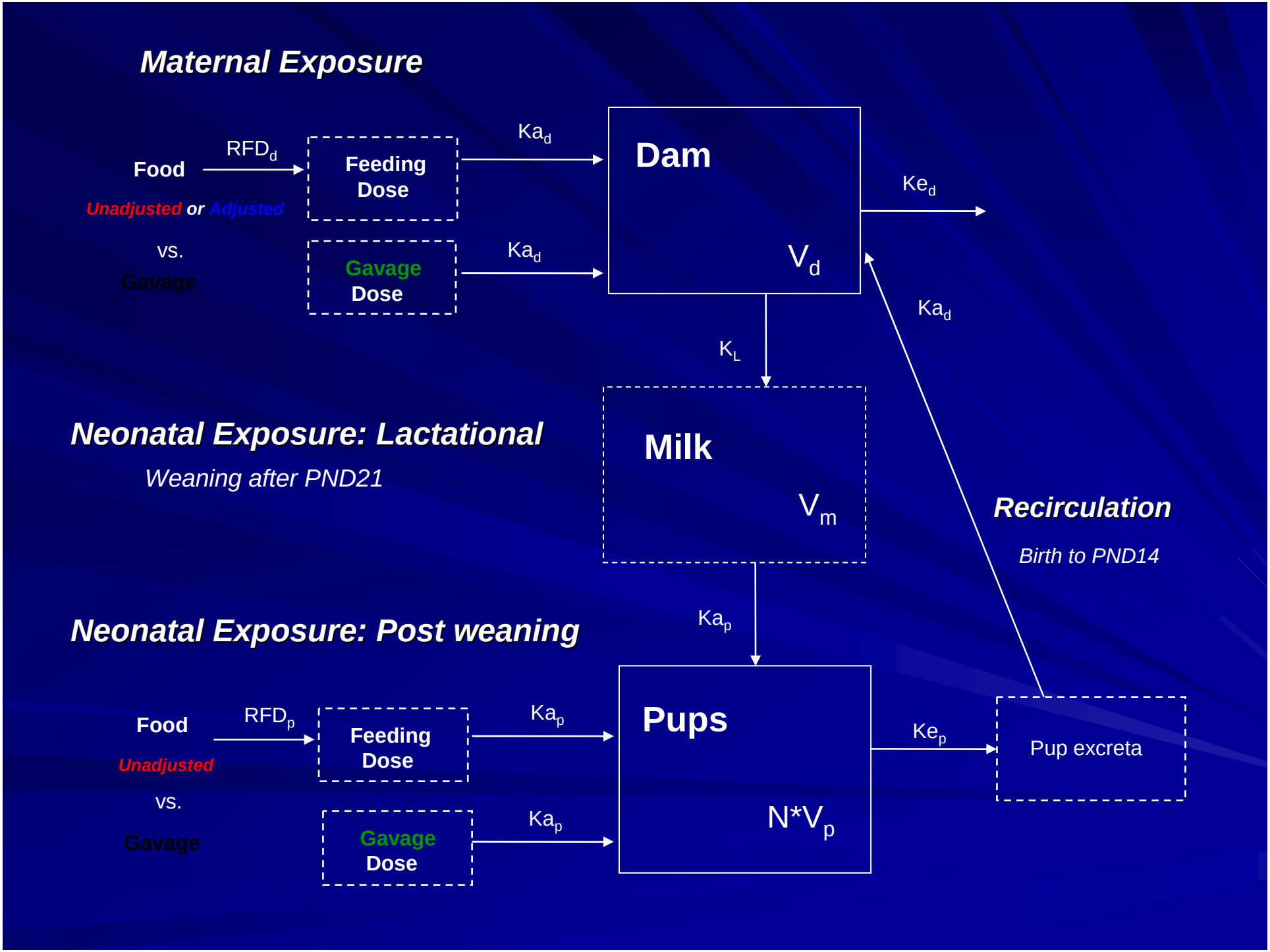




Lactational Modeling

- Toxicity studies
  - one- & two-generation reproductive/developmental, developmental neurotoxicity
- EPA uses average daily maternal dose (mg/kg/day) to assess potential risk to the mother and the offspring.
- How do pups' exposures compare to the dam's?
- Hypothesis: Pup exposures can be predicted from non-pregnant PK, milk partitioning, and scientific literature on growth.

Yoon, M. and Barton, H.A. (2007) Predicting maternal rat and pup exposures: How different are they? Toxicol Sci. doi: 10.1093/toxsci/kfm286

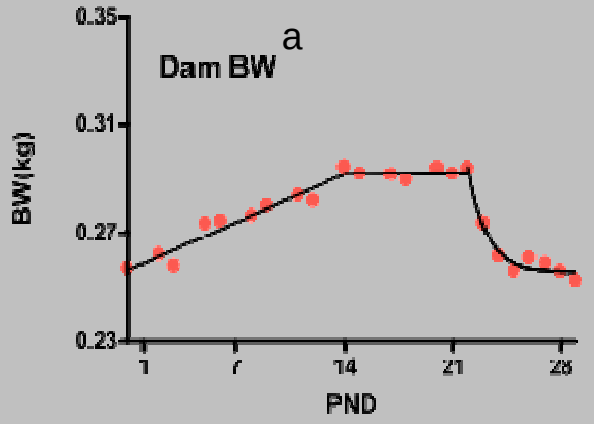

Maternal Exposure
Food
RFDd
Unadjusted or Adjusted
vs.
Gavage
Feeding Dose
Gavage Dose
Kad
Kad
Dam
Vd
Ked
Kad
KL
Milk
Vm
Neonatal Exposure: Lactational
Weaning after PND21
Recirculation
Birth to PND14
Neonatal Exposure: Post weaning
Kap
Food
RFDp
Unadjusted
vs.
Gavage
Feeding Dose
Gavage Dose
Kap
Kap
Pups
N*Vp
Kep
Pup excreta

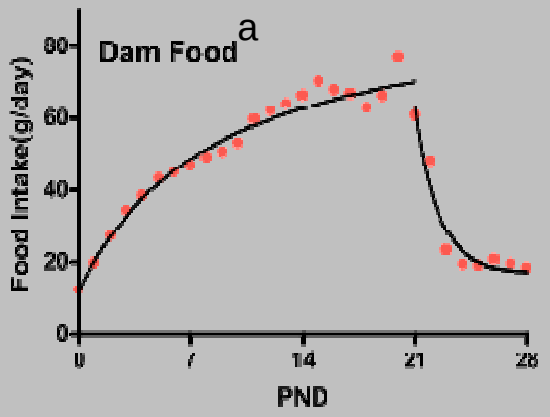
Biological Data Incorporated

- **Factors influencing maternal exposure during lactation**
  - Increase in dam body weight
  - Increasing dam food consumption
  - Excreta recirculation between dam and pup
- **Factors influencing pup exposure during lactation and early post-weaning**
  - Increase in pup body weight
  - Changing pup milk consumption during lactation
  - Constant suckling rate throughout the day
  - Consumption of solid food during late lactation
  - Higher rate of pup food consumption during post-weaning
  - Changes in pharmacokinetics (e.g. absorption, distribution, metabolism, excretion -> during rapid development, different from the dam)

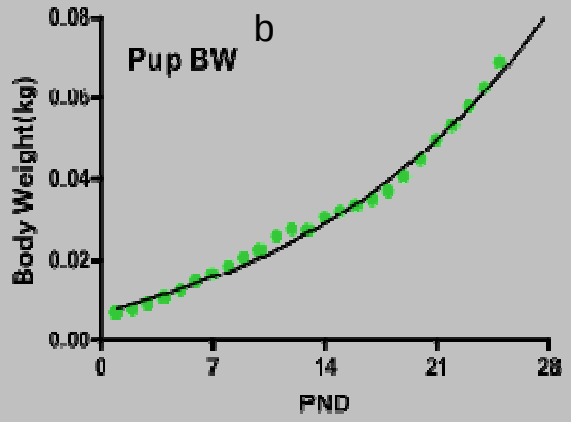
Biological parameter changes during post-natal period

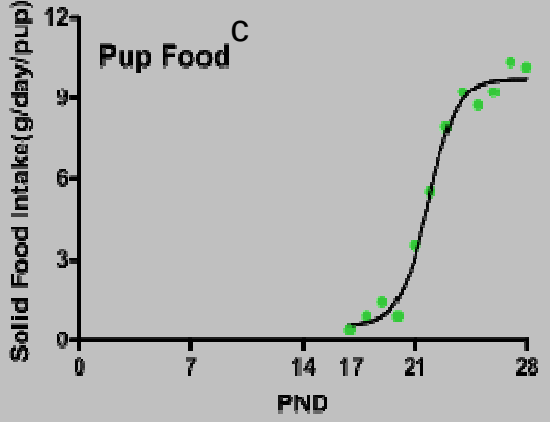
incorporated in the current model

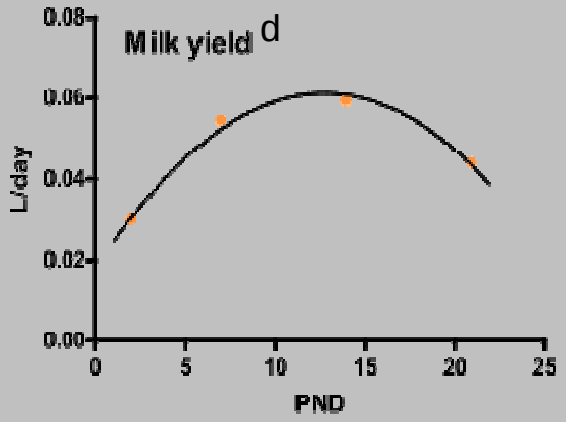




[a] Shirley, 1984
Lab. Animal Sci. 34:169-172
[b] Doerflinger and Swithers, 2004
Dev. Psychobiol. 45:72-82
[c] Redman and Sweney, 1976
J. Nutr. 106:615-626
[d] Knight et al., 1984
J. Dairy Res. 51:29-35

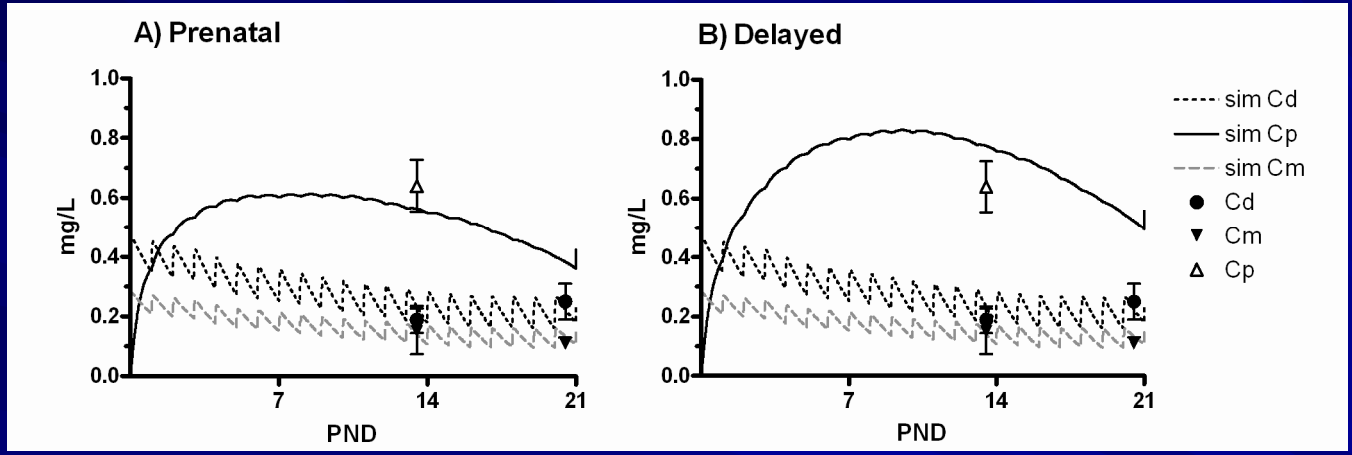






Modeling process

- Developed model from published literature
- Tested model against published data for ochratoxin A & 2,4-dichlorophenoxyacetic acid



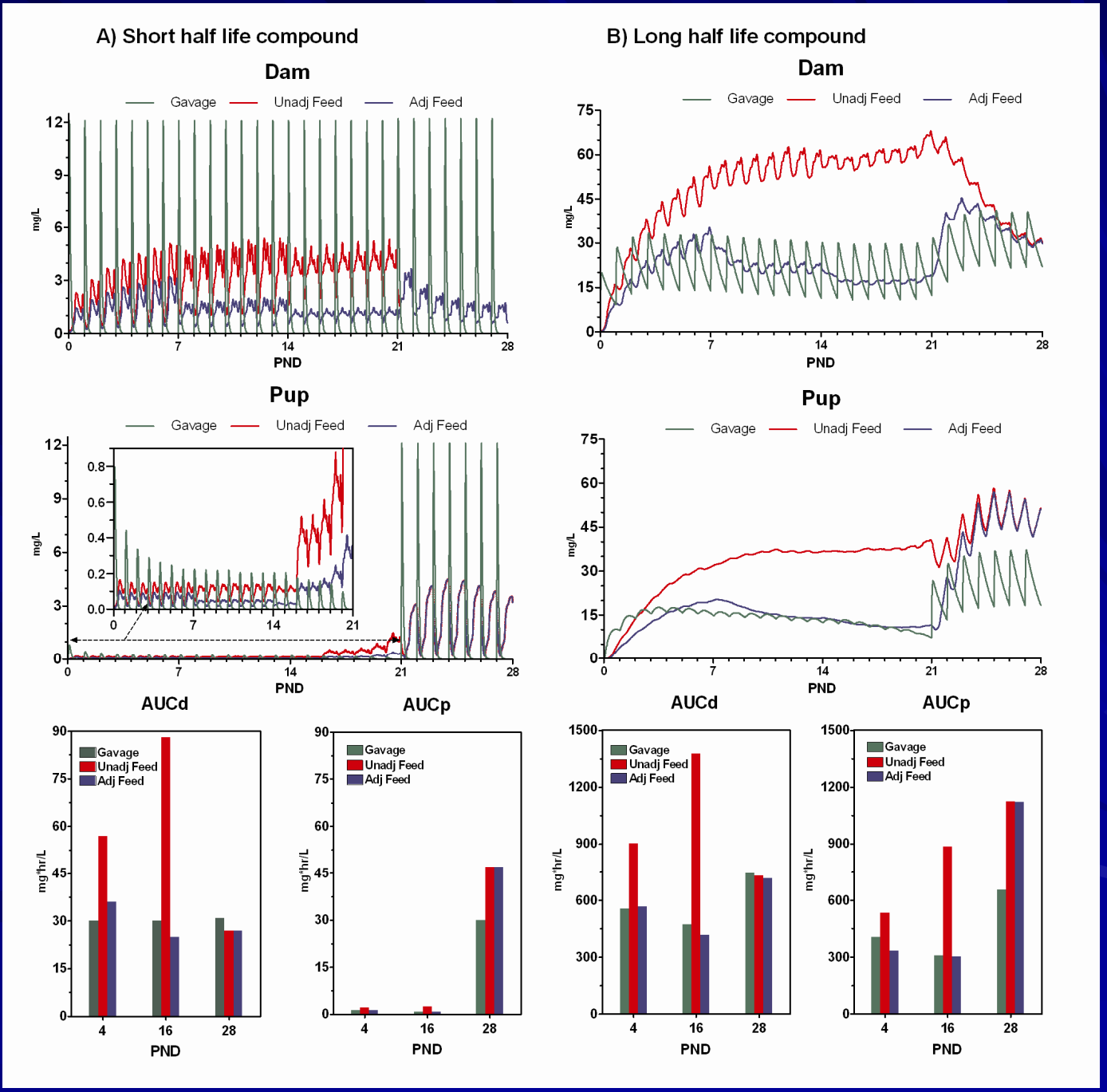
- Modeled 16 theoretical compounds
  - Half-lives: 1 & 24 hr
  - Vd: 0.2, 0.7, 2.5
  - Pm: 0.1, 1, 3, 10
  - Development of clearance (R) & excreta recirculation
  - Base cases: Vd_d=Vd_p=0.7, ka_d=ka_p,, 1 & 24 hr $t_{1/2}$, Pm=1, R=1,

Base Case

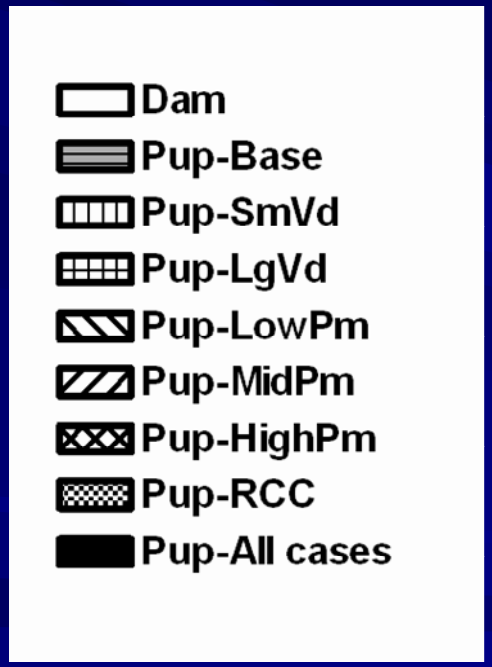
Half-lives

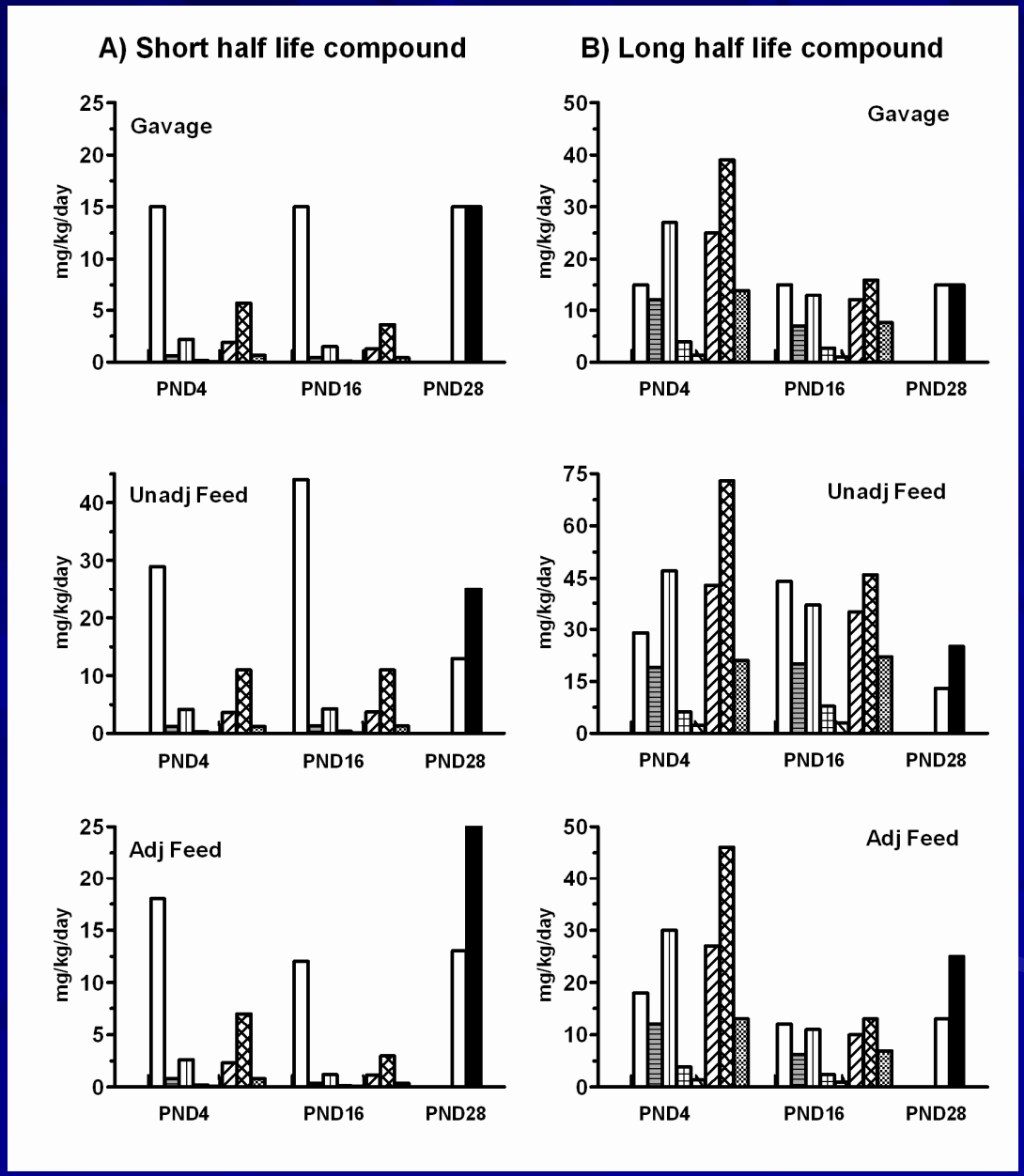
Short: 1 hr

Long: 24 hr



Predictions

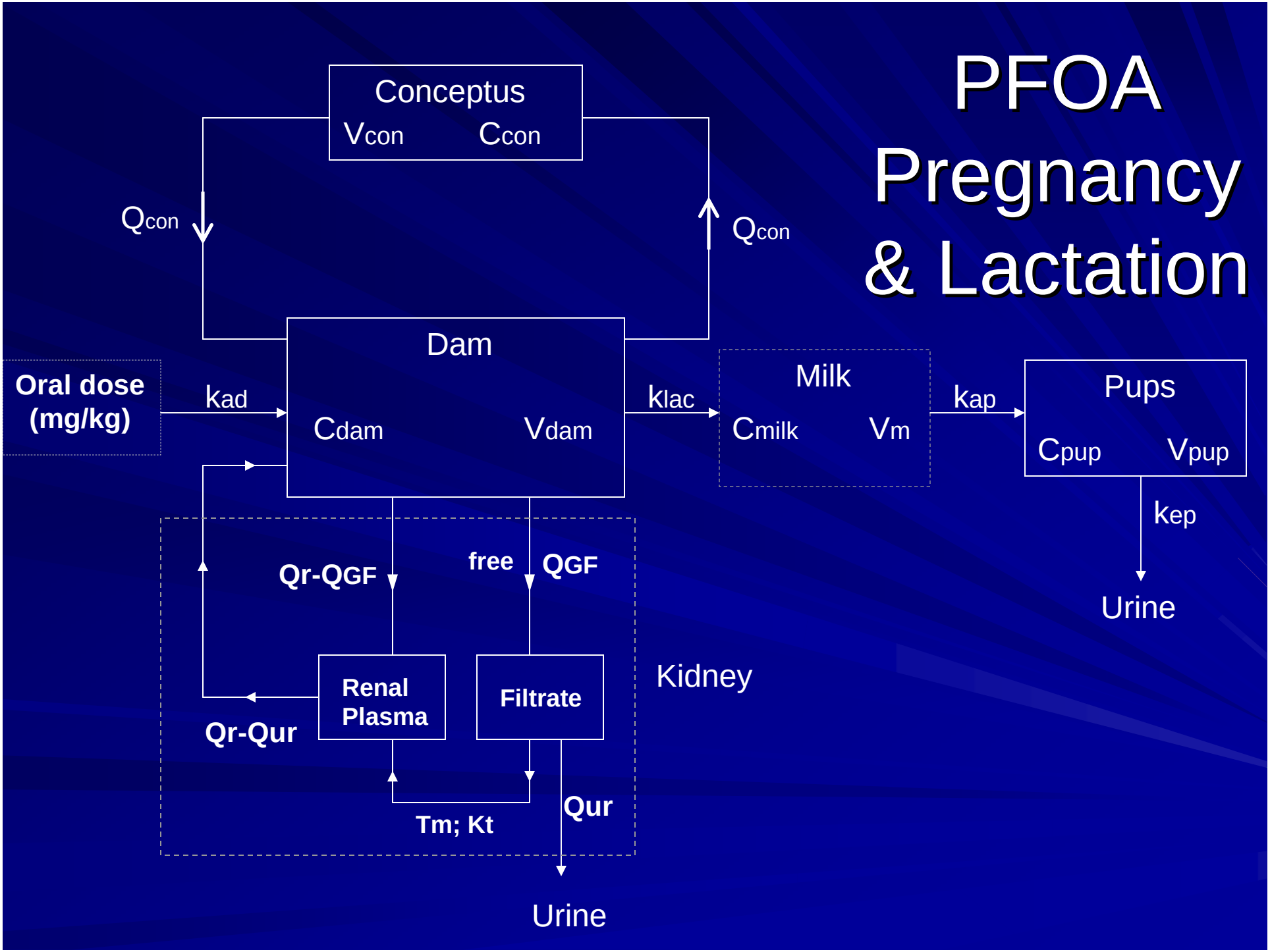




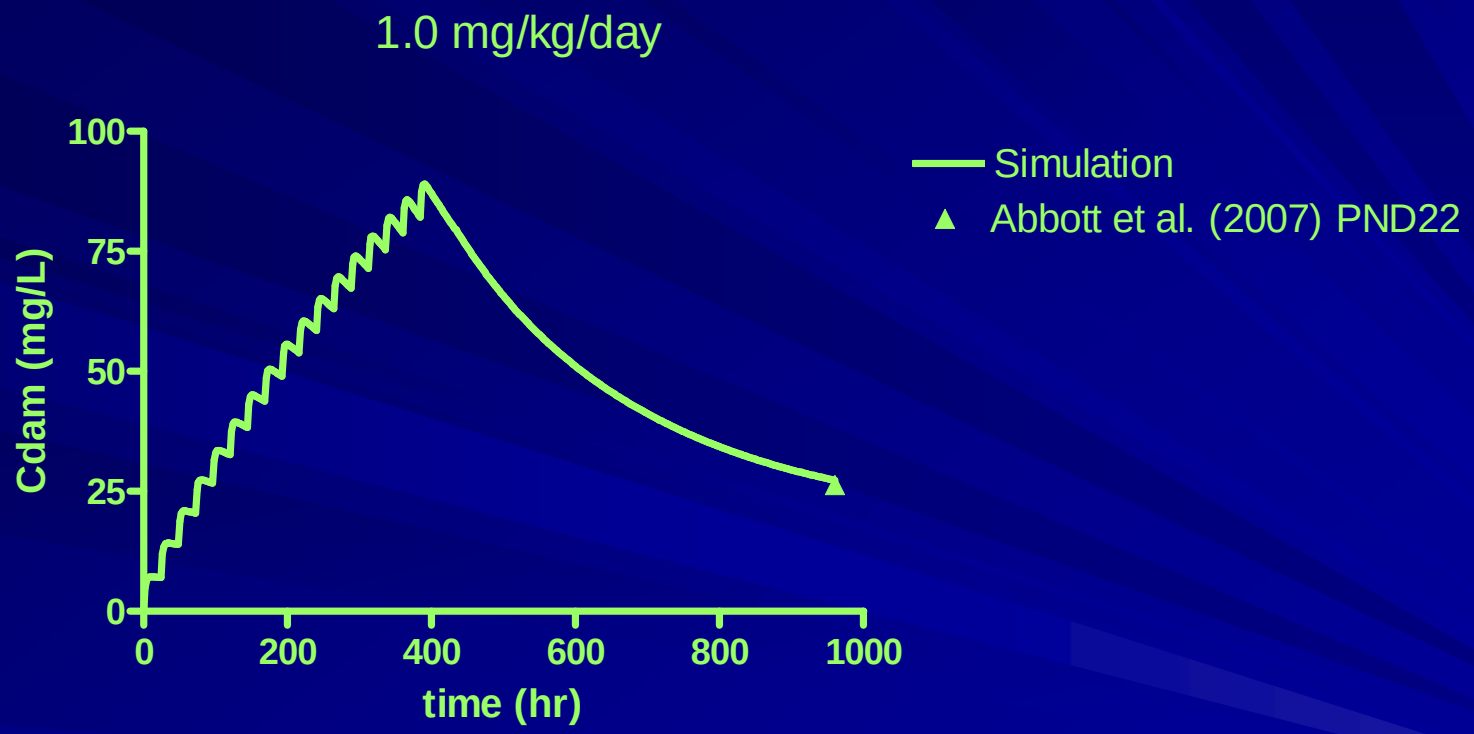
Lactational Dosimetry for PFOA

- Perfluorooctanoic acid
- Processing aid in manufacture of fluoropolymers & metabolite of some telomer alcohols
- Toxicity endpoints mice exposed in utero but observed postnatally (i.e., in utero and lactational dosimetry may be important)
- Single dose PK well fitted by one compartment model ($t_{1/2}$ ~ 15 days, Vd ~ 0.14 L/kg)
- Repeat dose inconsistent ($t_{1/2}$ ~ 1.5 days if Vd same)

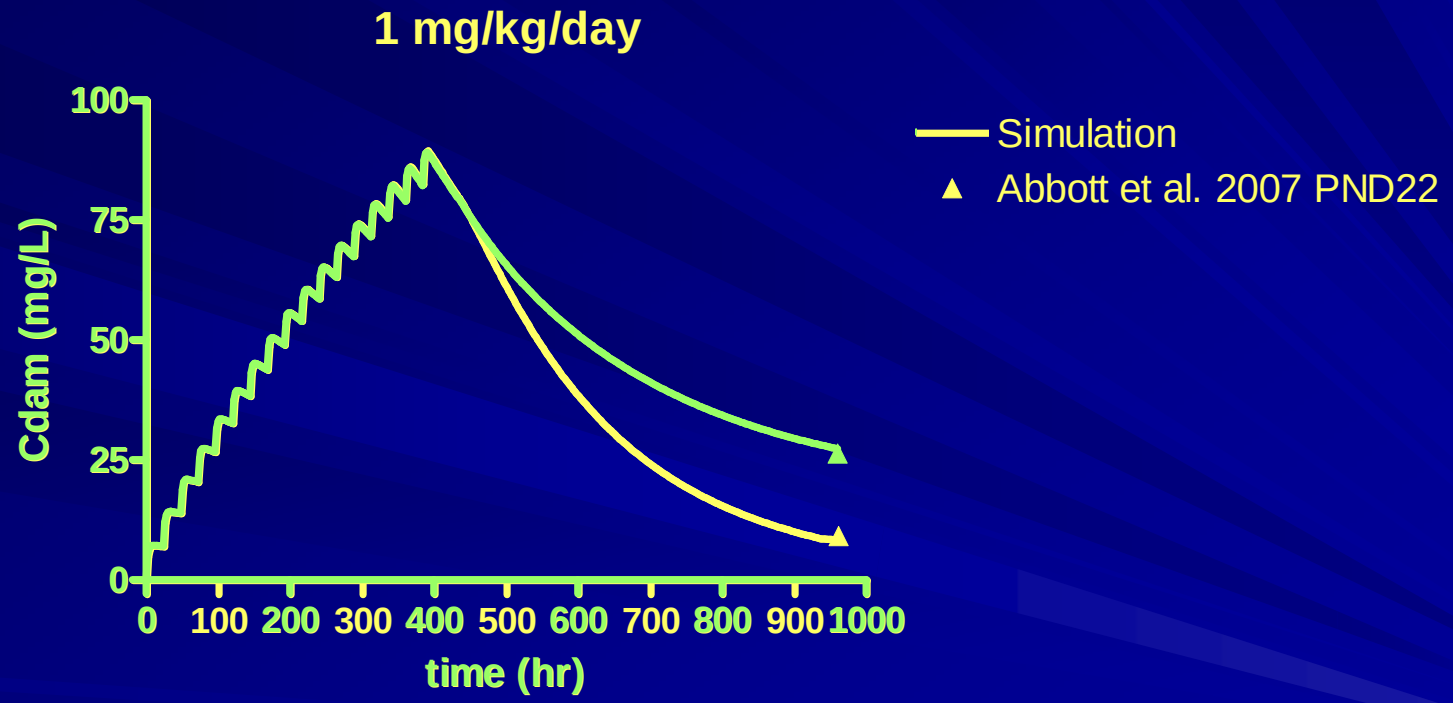
PFOA Pregnancy & Lactation



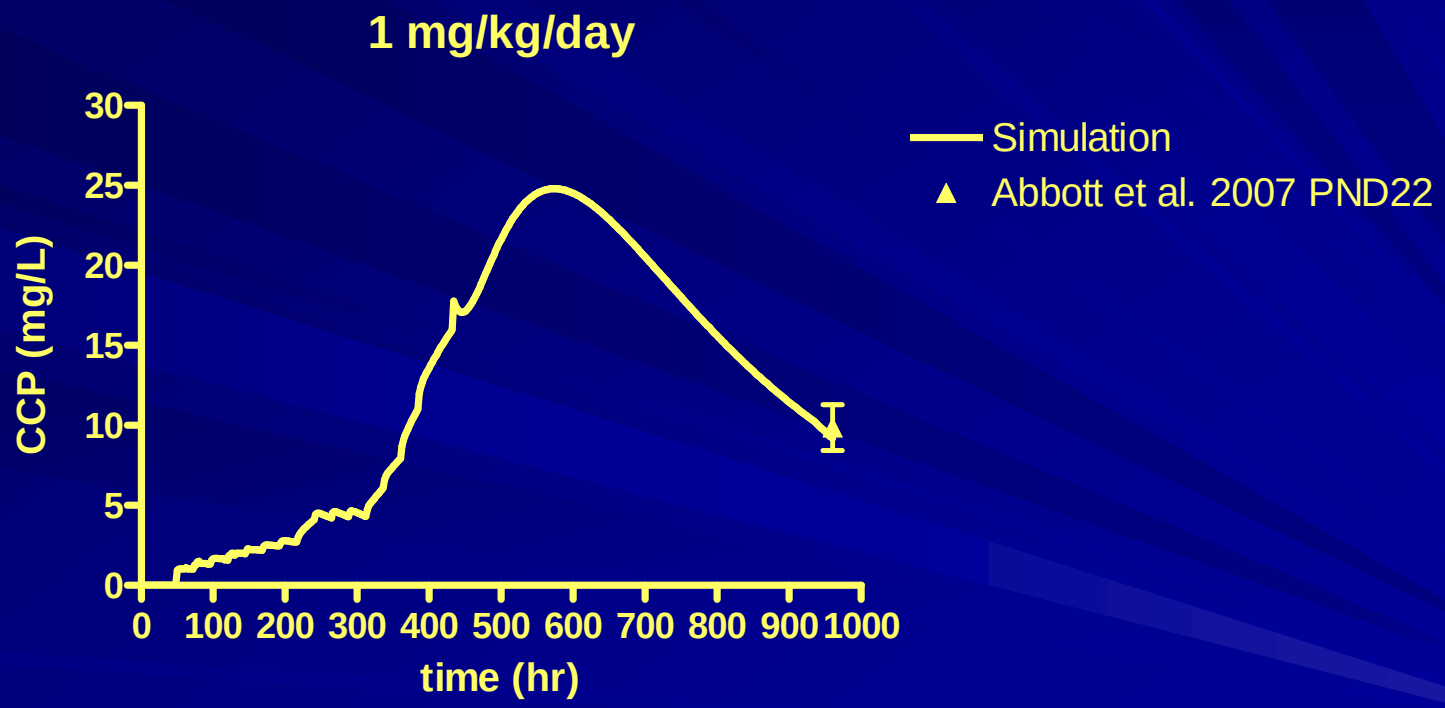
Simulation of Serum Levels in Non-Lactating Female Mice Dosed from GD1-17



Simulation of Serum Levels in Lactating Female Mice Dosed From GD1-17

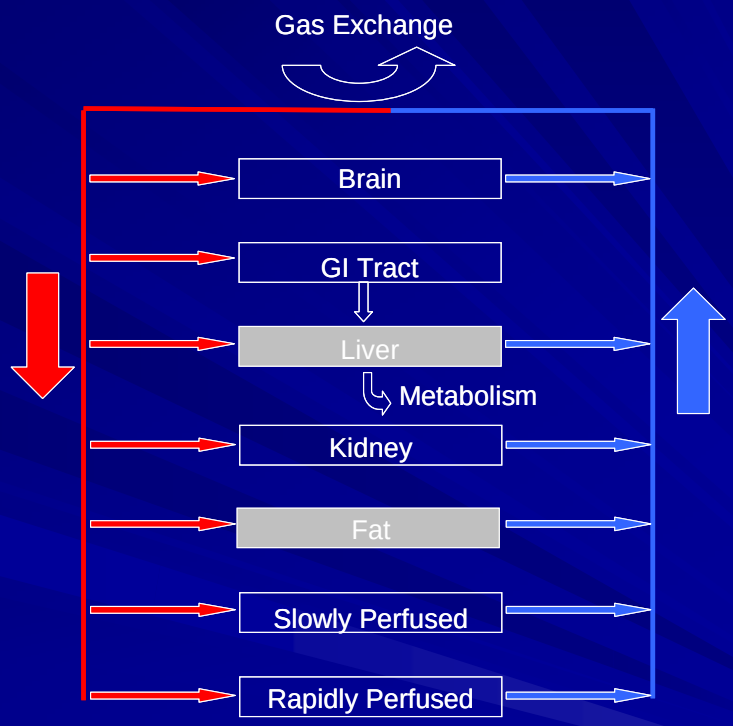


Simulation of Serum Levels in Conceptus/Pups From Lactating Female Mice Dosed From GD1-17

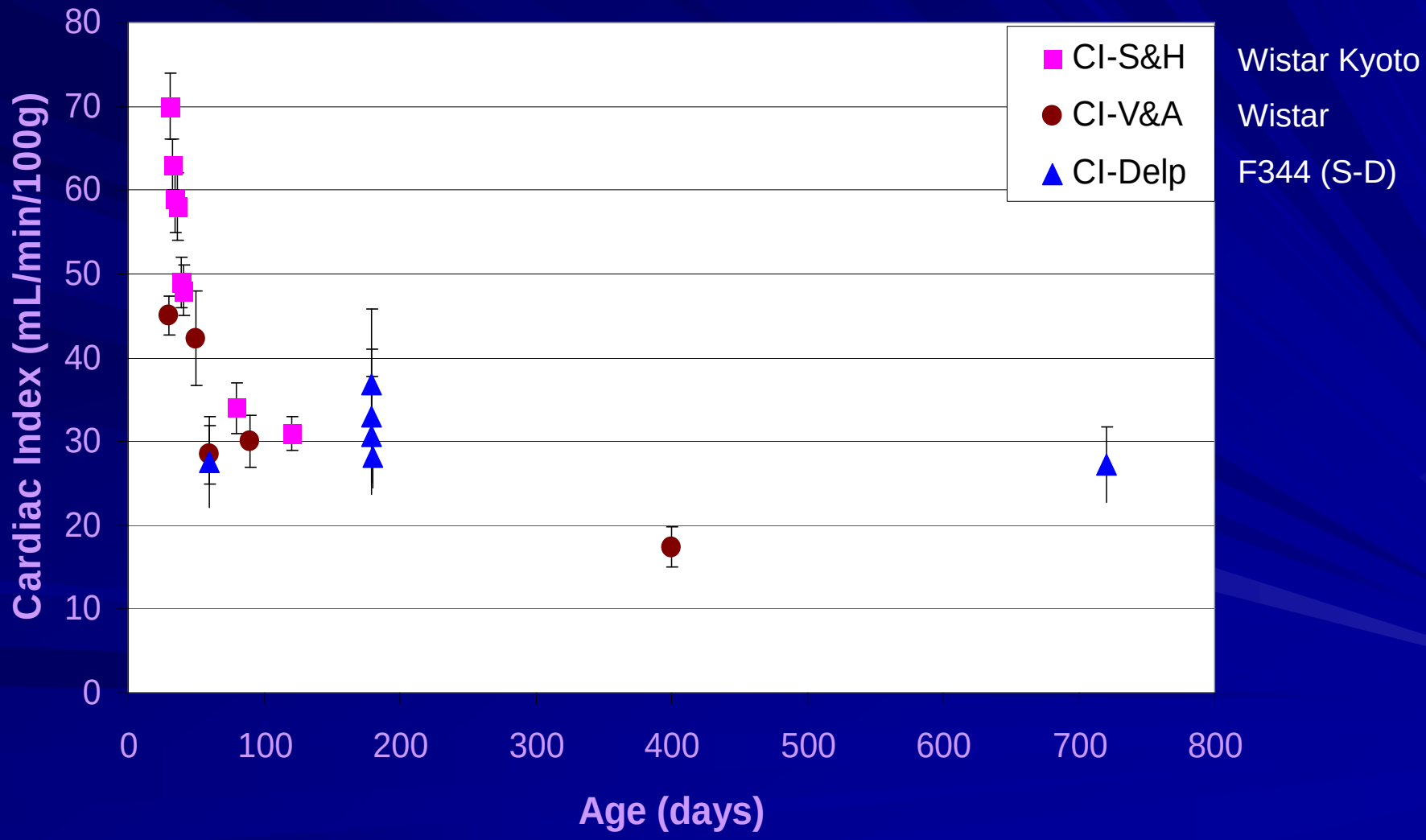


Age-dependent PK

- Predicting juvenile rat PK from adult and literature on development of relevant metabolizing enzymes
- Six volatile organic compounds ranging from highly lipophilic to highly water soluble



Cardiac Index vs Rat Age



Age-Adjustments for Metabolism

- Vmax & Km from PBPK models for adult rats
- Adjust to appropriate ages using in vitro data for substrates specific to enzymes (e.g., CYP, GST)

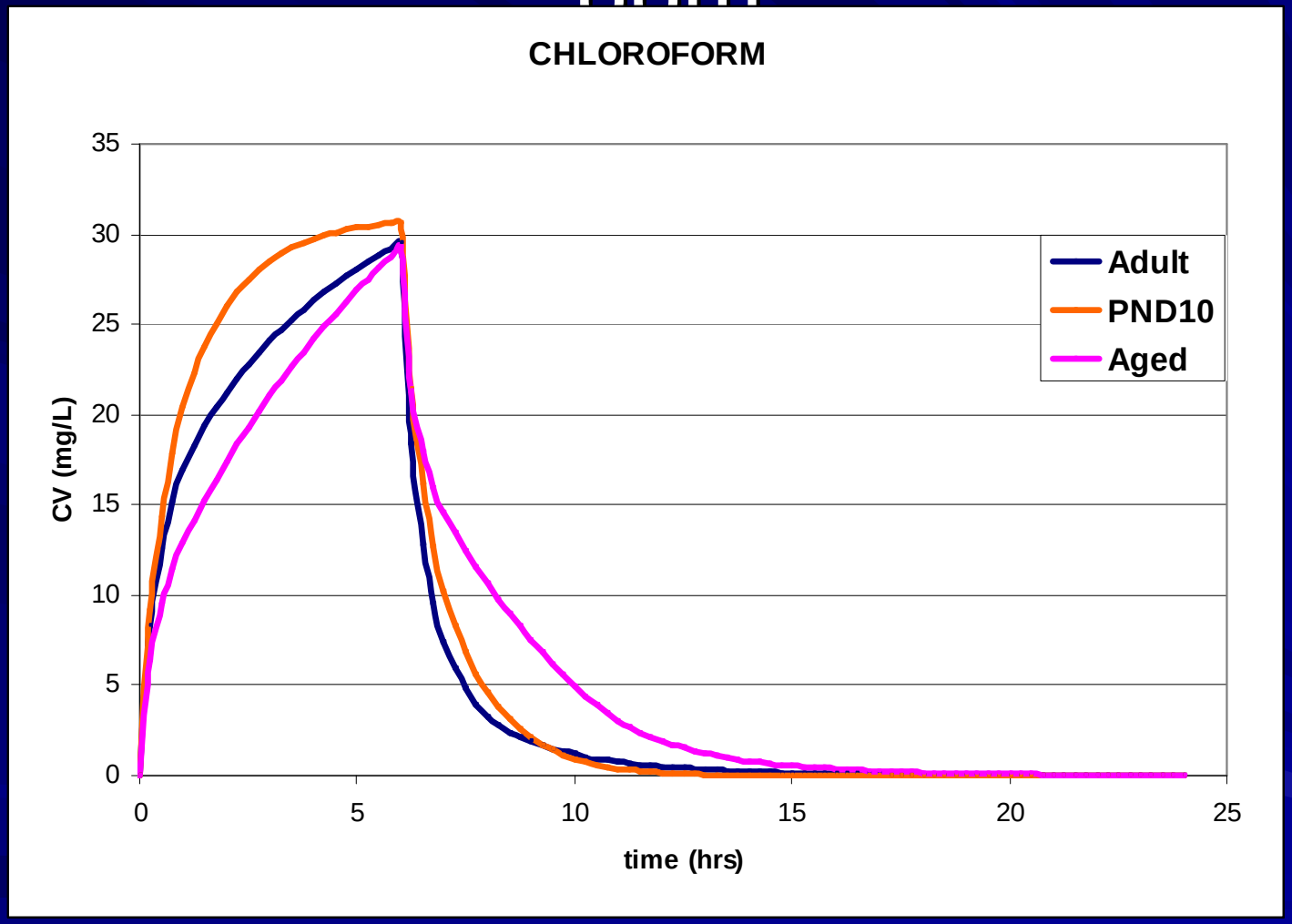
$$Vmax = Vmax(\text{in vitro})^{*}\ Cmp\ ^{*}VL$$

$$Vmax_{x} = Ra^{*}Rmp^{*}Rvl\ ^{*}Vmax_{adult}$$

$$Ra = \frac{(\text{CYP2E1 activity})_{x}}{(\text{CYP2E1 activity})_{adult}} \qquad Rmp = \frac{Cmp_{x}}{Cmp_{adult}} \qquad Rvl = \frac{VL_{x}}{VL_{adult}}$$

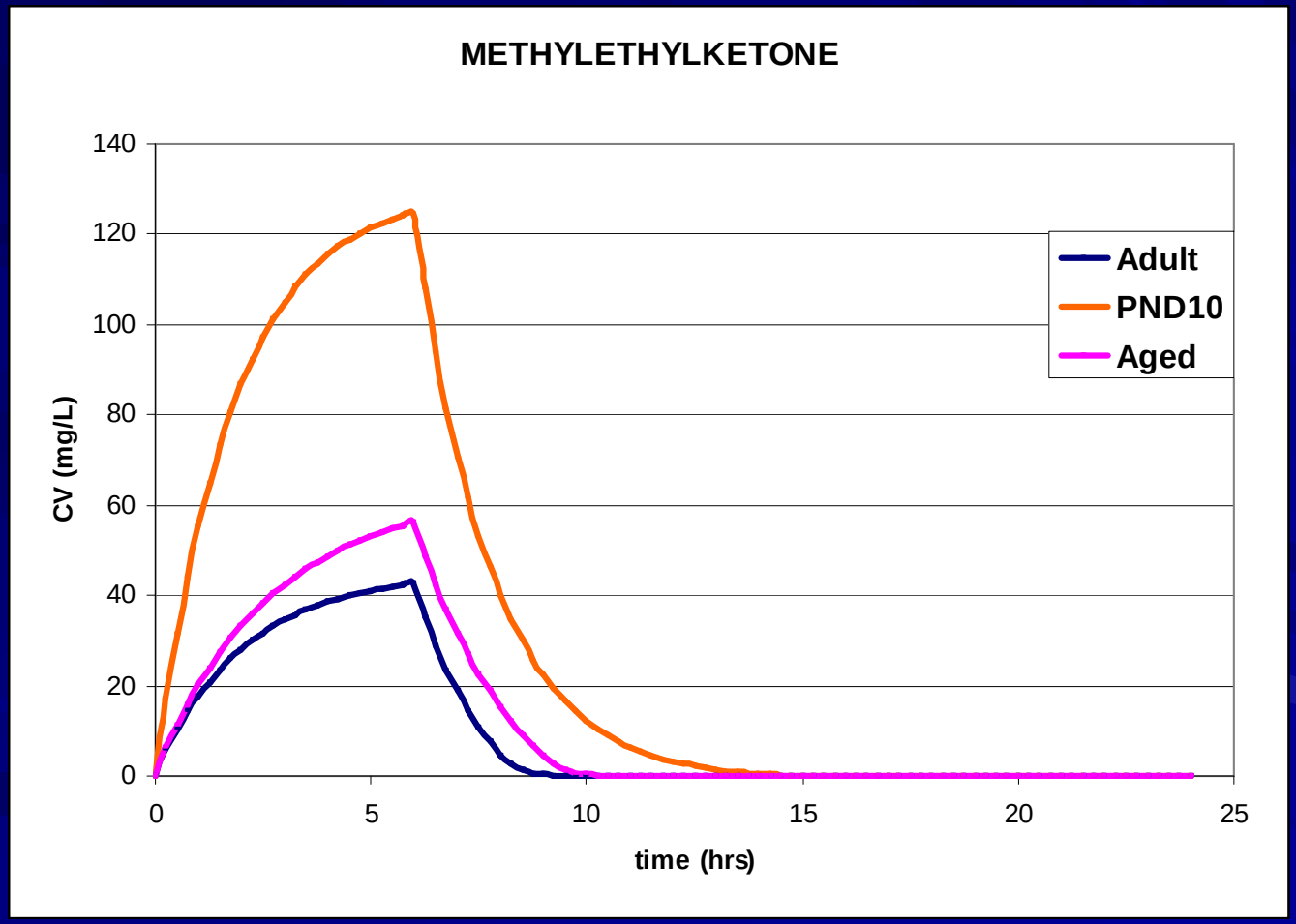
Ra*Rmp*Rvl = 0.042 and 1.09 for PND10 and aged rats

Chloroform: Rats – 6 hr, 500 ppm

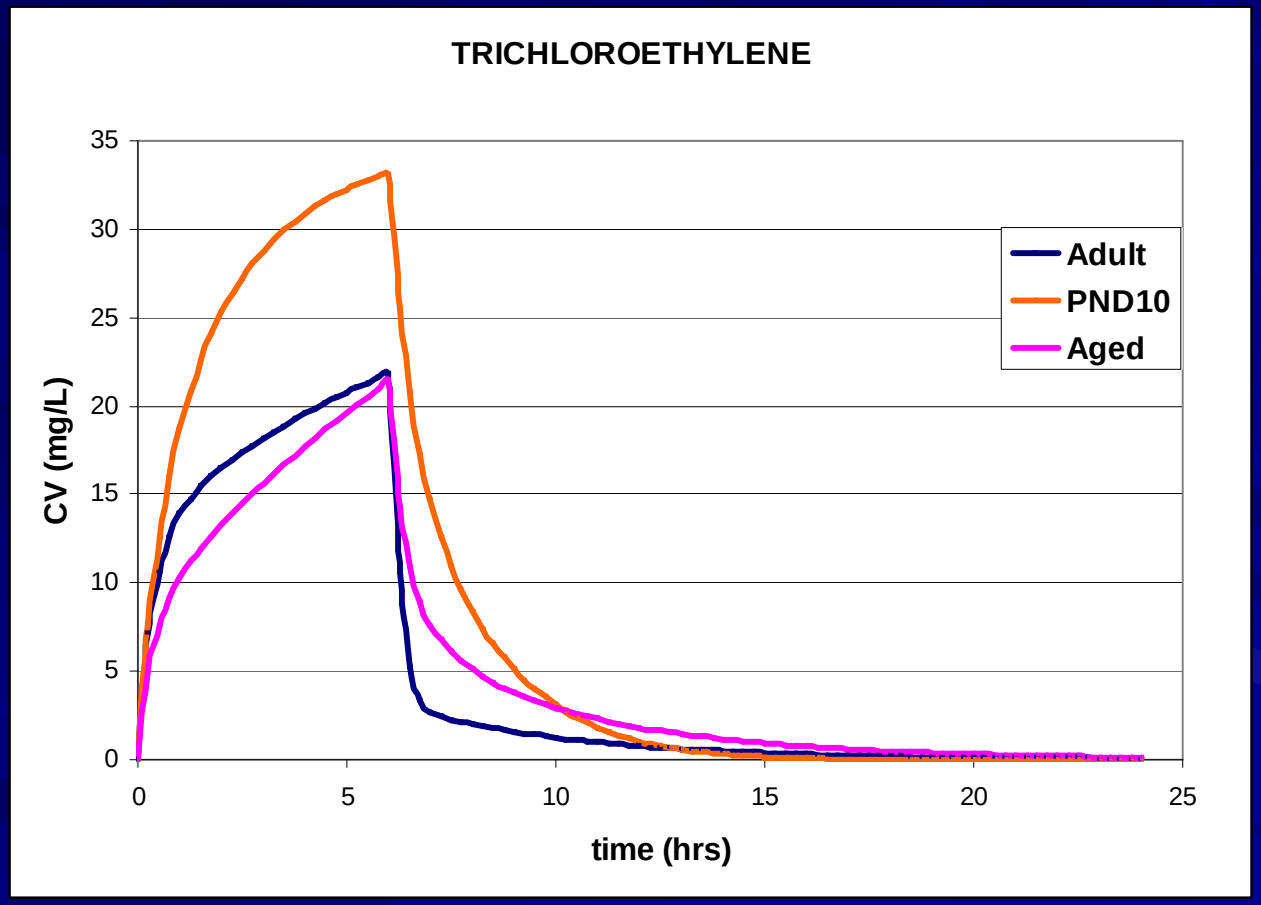


Venous Concentration of VOCs After a 500 ppm Exposure for 6 Hours

Methyl Ethyl Ketone: Rats – 6 hr, 500 ppm

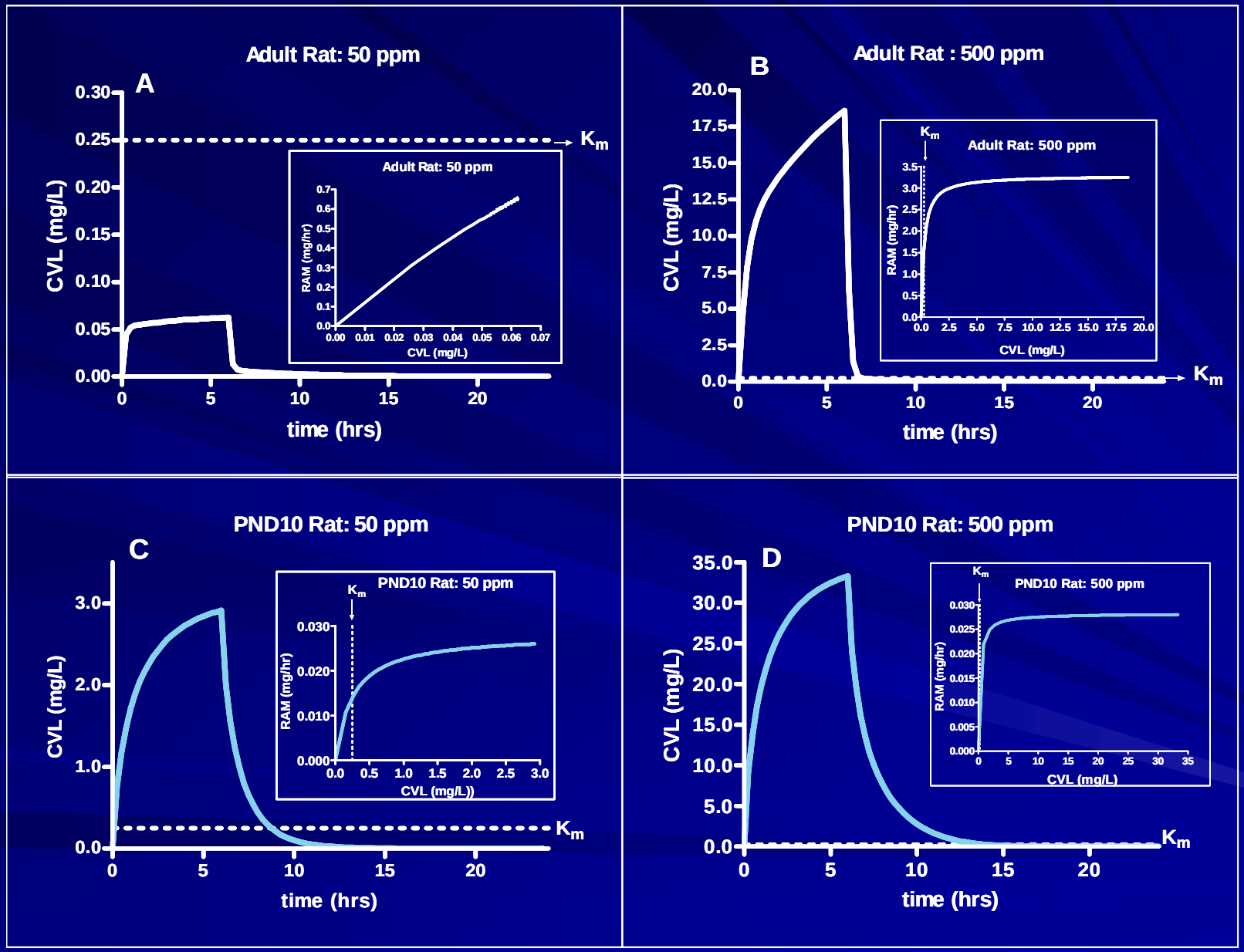


Trichloroethylene: Rats – 6 hr, 500 ppm

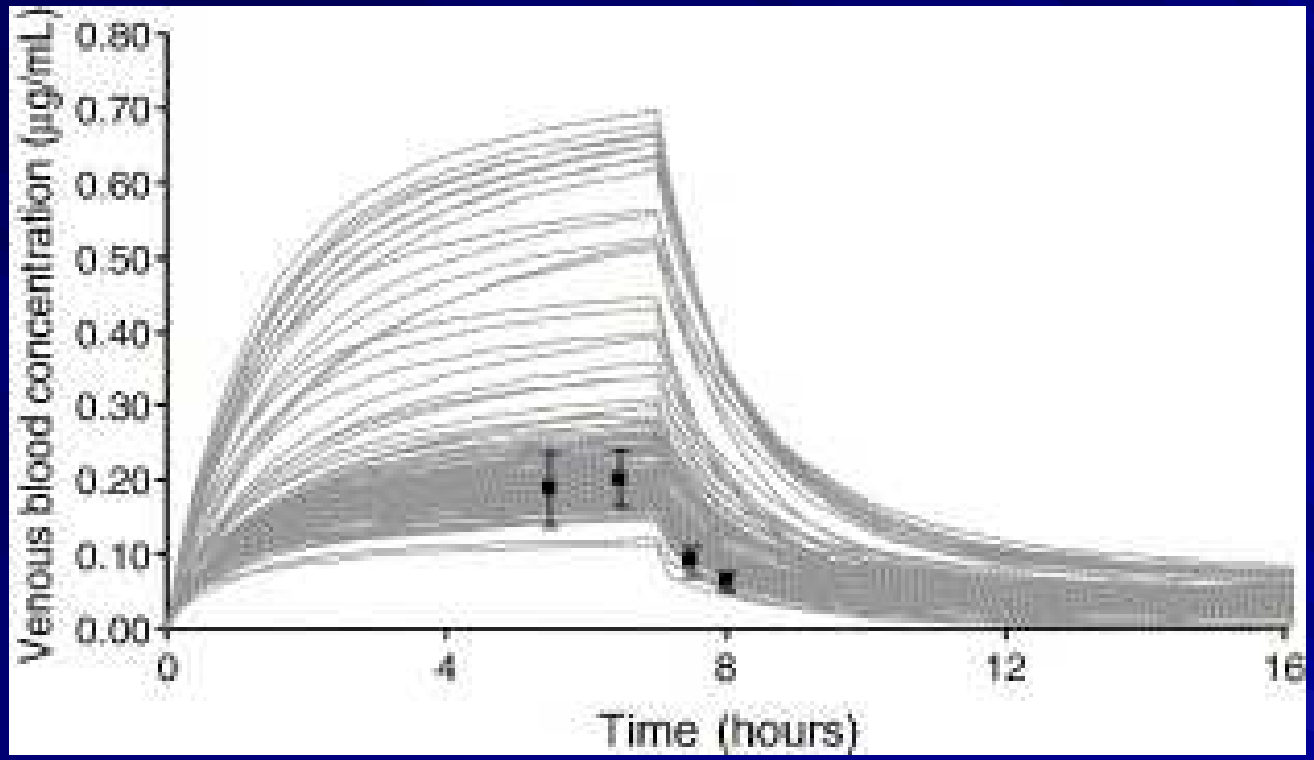


Predicted Amount of VOC Metabolized per Unit Liver Volume (mg/L) for Different Ages of the Rat at 24 h following a 50 or 500 ppm Inhalation Exposure for 6 h

VOC		PND10	Adult	Aged	Aged /Adult	PND10 /Adult
Perchloroethylene	500 ppm	12	104	97	0.9	0.1
	50 ppm	1.2	10.4	9.7	0.9	0.1
Trichloroethylene	500 ppm	635	2900	3909	1.3	0.2
	50 ppm	390	420	506	1.2	0.9
Benzene	500 ppm	273	1530	1954	1.3	0.2
	50 ppm	66	195	240	1.2	0.3
Chloroform	500 ppm	317	2004	2661	1.3	0.2
	50 ppm	215	386	460	1.2	0.6
Methylene Chloride	500 ppm	143	1257	1772	1.4	0.1
	50 ppm	99	259	308	1.2	0.4
Methyl ethyl ketone	500 ppm	1461	2557	2987	1.2	0.6
	50 ppm	376	286	333	1.2	1.3


Adult Rat: 50 ppm
A
CVL (mg/L)
time (hrs)
Km
Adult Rat: 50 ppm
RAM (mg/hr)
CVL (mg/L)
Adult Rat : 500 ppm
B
CVL (mg/L)
time (hrs)
Km
Adult Rat: 500 ppm
RAM (mg/hr)
CVL (mg/L)
PND10 Rat: 50 ppm
C
CVL (mg/L)
time (hrs)
Km
PND10 Rat: 50 ppm
RAM (mg/hr)
CVL (mg/L))
PND10 Rat: 500 ppm
D
CVL (mg/L)
time (hrs)
Km
PND10 Rat: 500 ppm
RAM (mg/hr)
CVL (mg/L)

Modeling Population Variability



Nong A, McCarver DG, Hines RN, Krishnan K. Modeling interchild differences in pharmacokinetics on the basis of subject-specific data on physiology and hepatic CYP2E1 levels: a case study with toluene. Toxicol Appl Pharmacol. 2006 214(1):78-87.

Fig. 5. Inhalation PBPK model simulations of venous blood concentrations in children (n = 116; from birth to 17 years old) exposed for 7 h to 17 ppm of toluene. This exposure concentration and duration correspond to those of a previous study in which adult volunteers were exposed to toluene for collection of data on blood concentrations (represented as symbols) (Tardif et al., 1997).

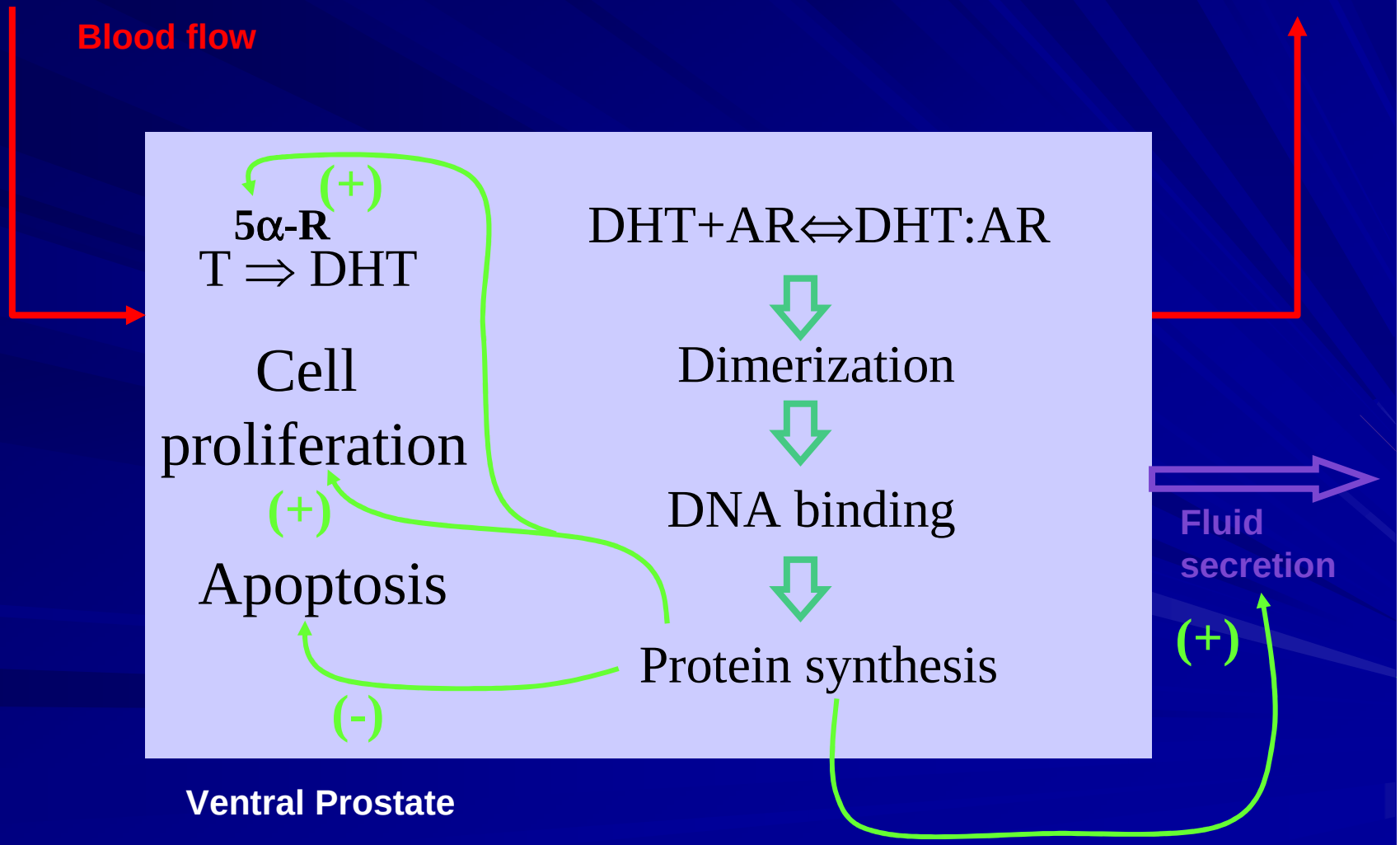
Prediction PD

- Prostatic Androgen Regulation
- Virtual Tissues

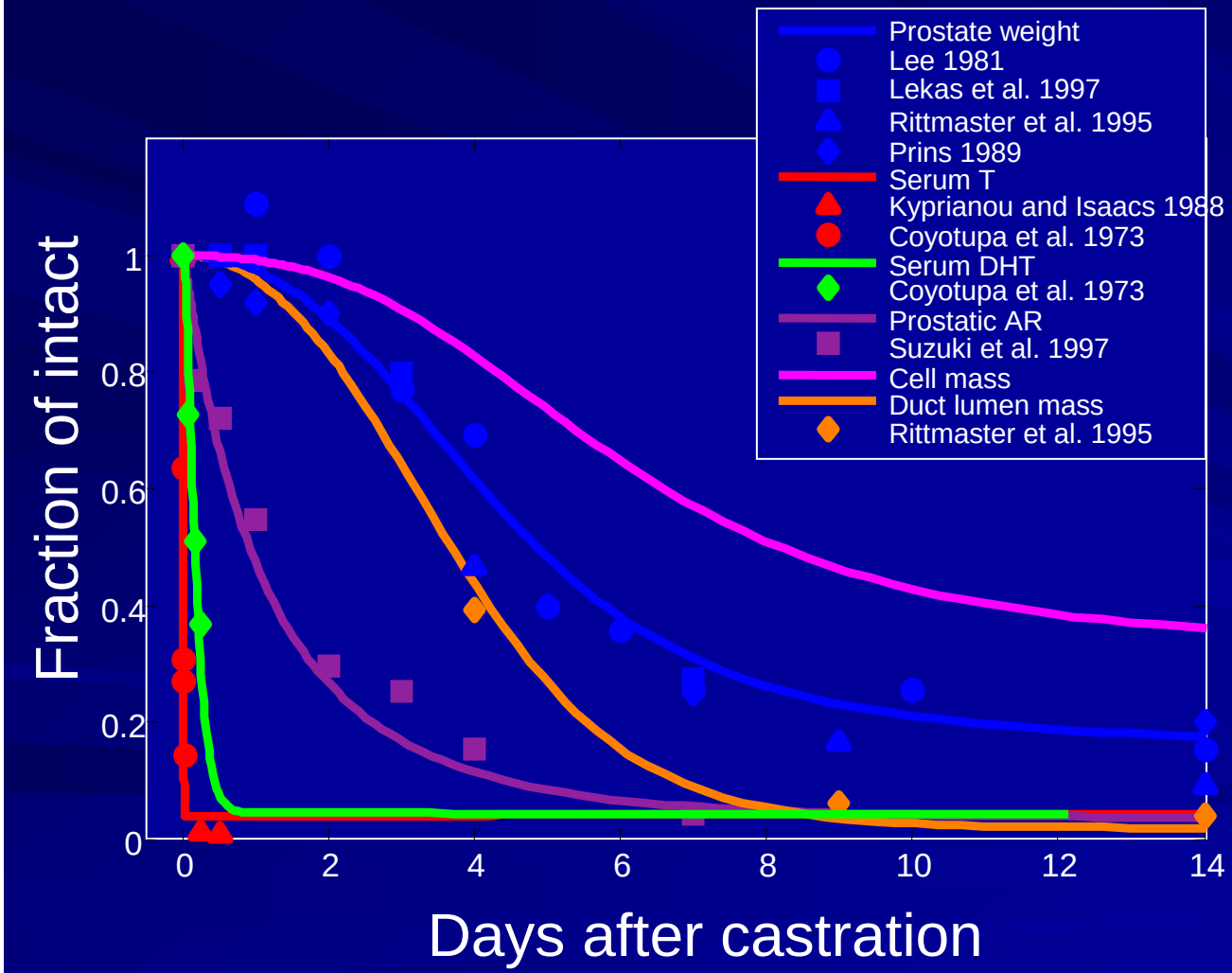
Androgen Regulation Modeling

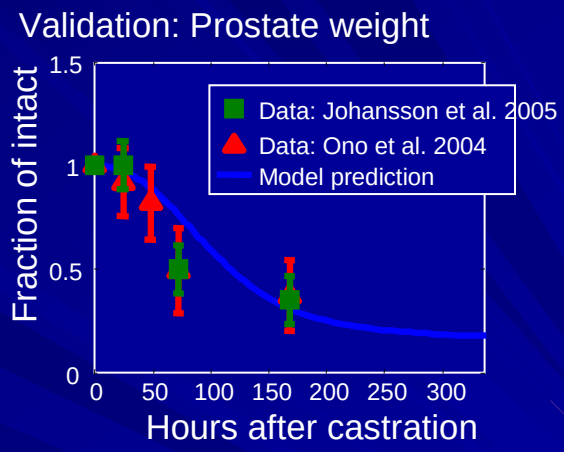
- Pharmacokinetics models
  - PBPK: testosterone, dihydrotestosterone
  - PK: LH
- Pharmacodynamic models
  - LH:testosterone/DHT negative feedback loop
  - Prostate androgen dependence
    - 5α-Reductase
    - Cell proliferation
    - Apoptosis
    - Fluid production

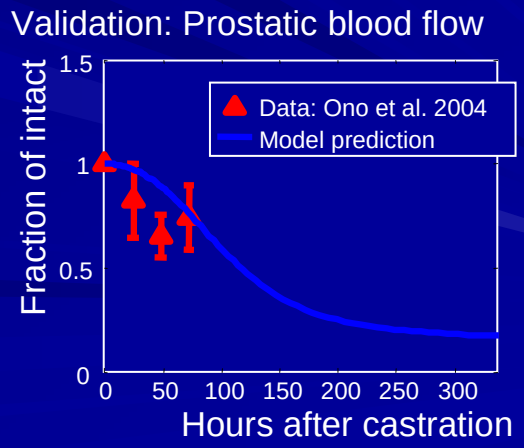
Prostate: Gene to Tissue Response

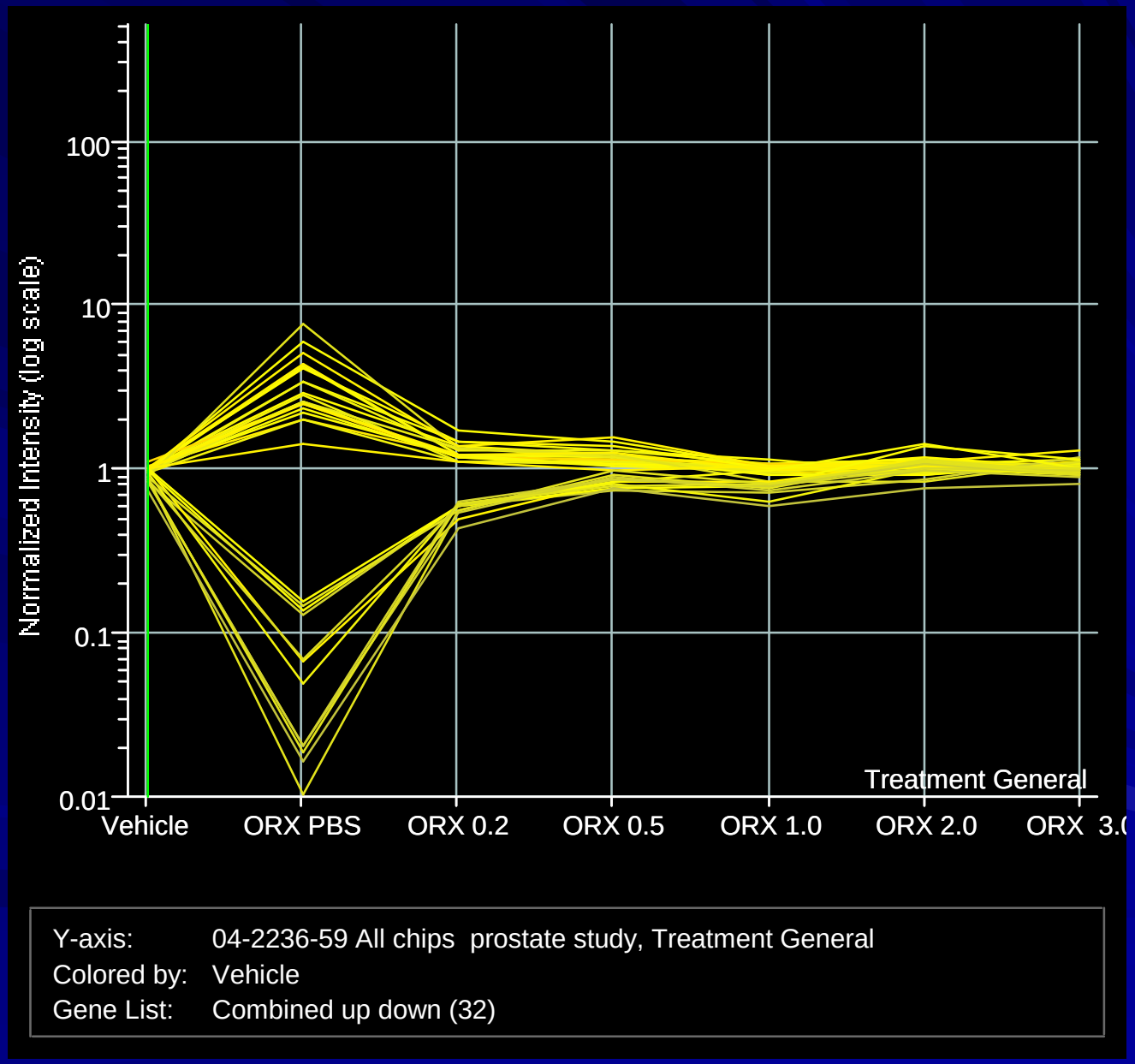


Predicted Prostate Regression Following Castration: Model Calibration and Validation

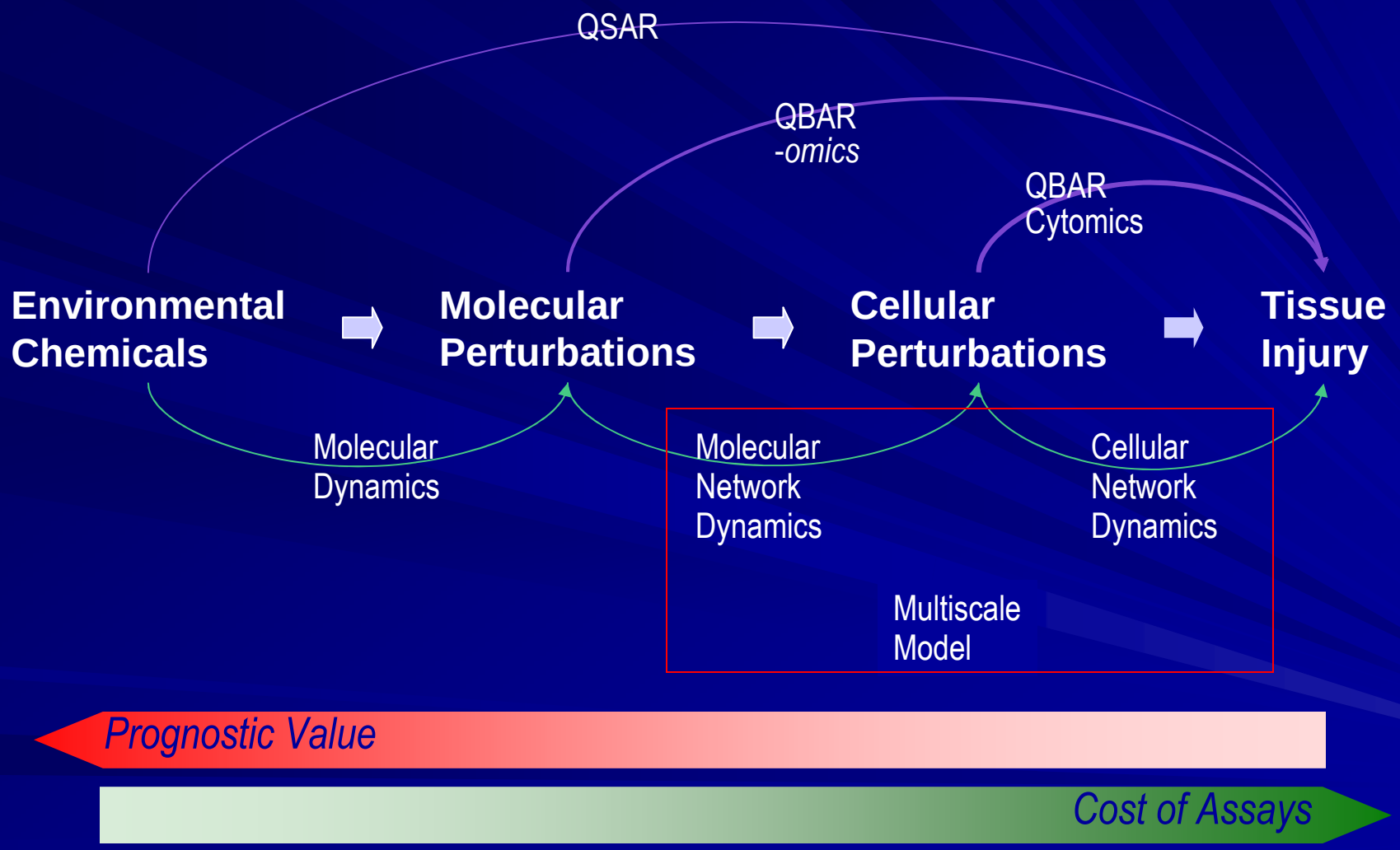




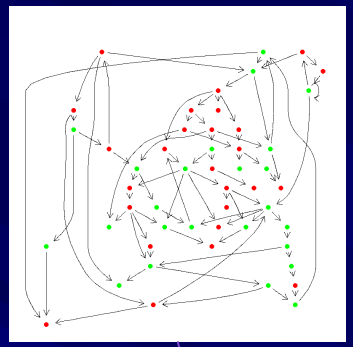


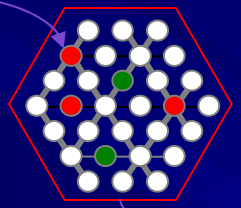

Normalized Intensity (log scale)
100
10
1
0.1
0.01
Vehicle
ORX PBS
ORX 0.2
ORX 0.5
ORX 1.0
ORX 2.0
Treatment General
Y-axis: 04-2236-59 All chips prostate study, Treatment General
Colored by: Vehicle
Gene List: Combined up down (32)

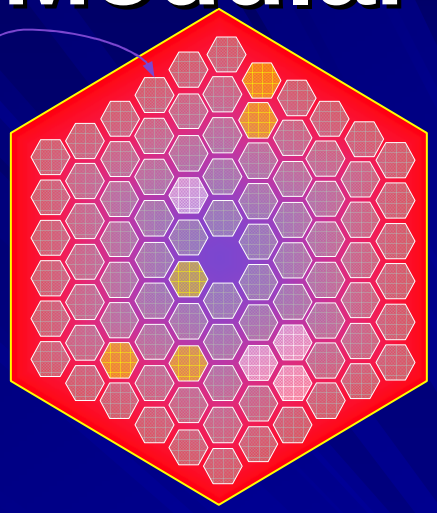
Approaches for Predicting Injury



Virtual Tissue Concept: Modular & Multiscale







I. Molecular Networks

Perturbation by exogenous & endogenous factors

II. Cell Response

Cellular response integrated over multiple modular subnetworks

III. Tissue Outcomes

Cellular network behaviour in nutrient / chemical gradient

Implement for NR-Mediated Hyperplasia

Nuclear receptor signaling
Xenobiotic metabolism
…

Cell Fate:
- Survival
- Death (Apoptosis)
- Division

Hyperplasia

Model Cell State: Apoptosis / Proliferation

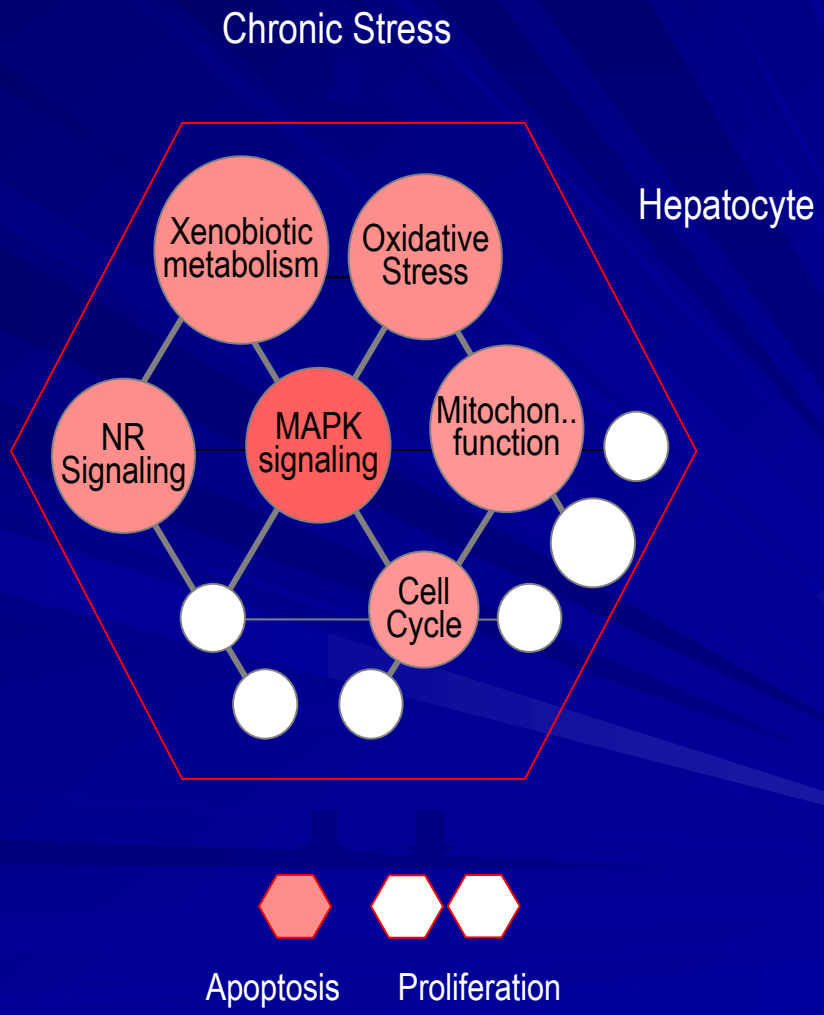
Focus on hepatocyte *hyperplasia*

Hyperplasia preceded by hepatocellular proliferation

Hyperplasia dynamic balance between cell death and division

Short-term: Model hepatocyte state using data on key-events in MoA

Long-term: Model cell state with dynamic molecular networks



Tissue Context: Hepatic Lobule

Heterogeneous structure

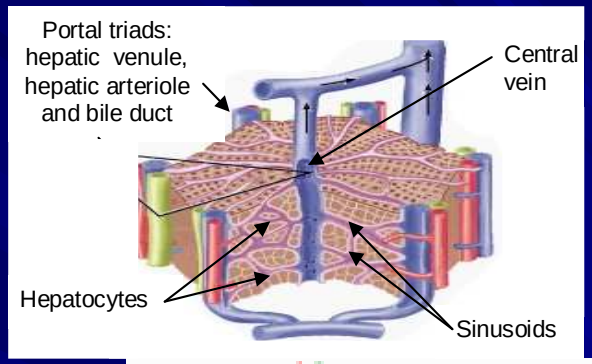
5 Cell types organized in a network around sinusoids

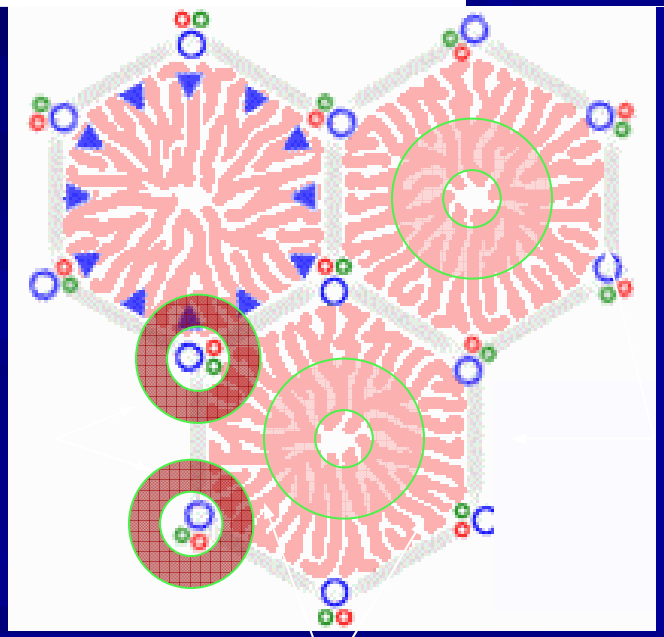
-Adaptation to gradients=> zones

-Zones are functionally different

-Injury can be zonal

Agent	*Necrosis*		
	1	*2*	*3*
Acetminophe n	-	-	+
$Fe_2(SO_4)_3$	+	-	-
Beryllium	-	+	-
Aflatoxins	+	-	+





1. Peritportal

2. Midzonal

3. Centrolobular

Zimmerman 1978

Meeks, Harrison & Bull, 2000 | jhu.edu

Regulatory Acceptance

- Acceptance within and outside an organization.
- What matters?
  - Transition from model developers (teams with deep knowledge and experience) to model users (for evaluation and/or implementation)
  - Educational process: Model overview for broad audience - What does it do?, How does it do it?
  - “Sharing” process: “Complete” documentation, instructions on how to run the model

Regulatory Acceptance

- Evaluation of biologically based models
  - PBPK Good Modeling Practice Workgroup, International Programme on Chemical Safety, World Health Organization (IPCS/WHO)
  - PK Working Group, National Center for Environmental Assessment (NCEA), ORD, US EPA
  - Model documentation, evaluation, communication to users

Vodovotz Y, et al. Evidence-based modeling of critical illness: an initial consensus from the Society for Complexity in Acute Illness.J Crit Care. 2007 Mar;22(1):77-84.

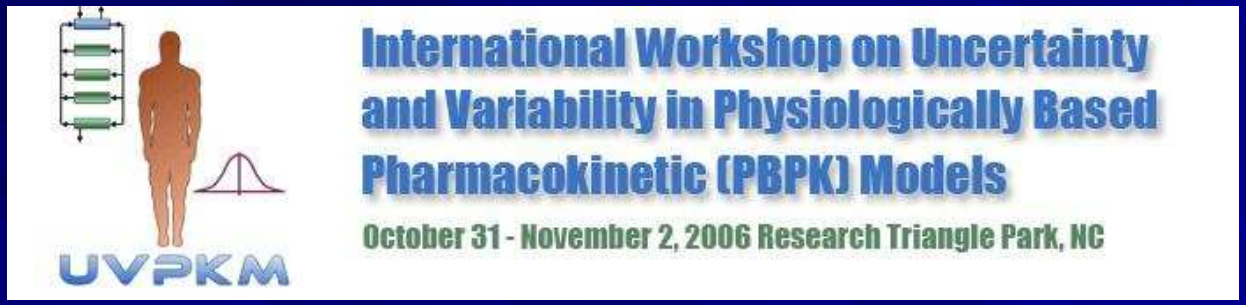
Regulatory Acceptance

- Evaluation of biologically based models
  1. Model Purpose
  2. Model structure & biological characterizations
  3. Mathematical descriptions
  4. Computer implementation
  5. Parameter analysis
  6. Comparison of model and data
  7. Specialized analyses: population variability, sensitivity analyses

Clark, L.H., Setzer, R.W. and Barton, H.A. (2004) Framework for Evaluation of Physiologically-Based Pharmacokinetic Models for Use in Safety or Risk Assessment. Risk Anal 24, 1697-1718.

Regulatory Acceptance

- Characterizing uncertainty and variability



  - Statistical calibration including Bayesian approaches using Markov Chain Monte Carlo methods
  - Local and global sensitivity analyses to characterize model behavior

Barton, H.A., et al. (2007) Characterizing Uncertainty and Variability in Physiologically-based Pharmacokinetic (PBPK) Models: State of the Science and Needs for Research and Implementation. Toxicol Sci 99(2):395-402

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